



NOTES

CONNECTIVE TISSUE DISORDERS

GENERALLY, WHAT ARE THEY?

PATHOLOGY & CAUSES

- Genetic disorders affecting synthesis of connective tissue components (e.g. fibrillin, collagen)
- Genetic mutation → dysfunctional protein (e.g. ↓ function fibrillin/collagen) → ↓ supportive function connective tissue → ↓ function of various organs, tissues
- Common disorders
 - Marfan syndrome (fibrillin 1 mutation)
 - Ehler–Danlos syndrome (various etiologies)
 - Osteogenesis imperfecta (collagen Type I mutation)
 - Alport syndrome (collagen Type IV mutation)
- Vary from dominant to recessive, range in severity

SIGNS & SYMPTOMS

- May affect all organ systems containing connective tissue; esp. musculoskeletal, ocular, cardiovascular systems

DIAGNOSIS

OTHER DIAGNOSTICS

- Standardized criteria
- Genetic testing (confirmation)

TREATMENT

OTHER INTERVENTIONS

- Supportive due to the genetic basis of disease, not curable

CONNECTIVE TISSUE DISORDERS OVERVIEW

	ALPORT SYNDROME	EHLERS–DANLOS SYNDROME	MARFAN SYNDROME
PROTEIN AFFECTED	Collagen Type IV	Collagen	Fibrillin 1
GENE MUTATION	Various COL4 genes	30 mutations identified	FBN1
INHERITANCE TYPE	Varies	Autosomal dominant/ recessive	Autosomal dominant
TISSUES MAJORLY AFFECTED	Basement membranes of glomeruli, ears, eyes	Skin, ligaments, bones, cardiovascular	Eyes, skeleton, heart, skin

VISIT...

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ALPORT SYNDROME

osms.it/alport-syndrome

PATHOLOGY & CAUSES

- Rare disorder caused by mutations in genes encoding for chains of Type IV collagen → abnormal basement membranes of kidney glomerulus, eye, cochlea
 - AKA hereditary nephritis
- Mutation substitutes glycine with different amino acid → triple-helix unable to form → impaired basement membrane structure
 - Glomerular basement membrane progressively hardens as abnormal Type IV collagen accumulates → thin glomerular basement membrane nephropathy
 - Impaired ability of hair cells attached to basement membrane in organ of Corti (in cochlea) to generate nerve signals
 - Thinning of lens capsule → disruption of lens shape → anterior lenticonus

TYPES

X-linked

- COL4A5 on X-chromosome
- Presents early, most common form

Autosomal recessive/dominant

- COL4A3, COL4A4 mutations

Thin basement membrane nephropathy

- Mild mutations in COL4A3, COL4A5
- Microscopic hematuria (sole symptom)

RISK FACTORS

- Family history

COMPLICATIONS

- End-stage renal disease, sensorineural hearing loss, changes in visual acuity, aortic aneurysms

SIGNS & SYMPTOMS

- Generally appear in early childhood/adolescence
- Renal
 - Progressive renal insufficiency, hypertension
- Eye
 - Corneal abrasions, lens opacity, ocular pain
- Ear
 - Initial high-frequency hearing loss → loss of normal speech

DIAGNOSIS

LAB RESULTS

Urinalysis

- Hematuria, proteinuria, ↑ creatinine

OTHER DIAGNOSTICS

Clinical exam

- Renal failure with deafness, with no other apparent cause

Ophthalmic examination

- Slit lamp examination of eye
 - “Oil droplet” reflex
- Fundoscopy
 - White/yellow granulations in retina (fleck retinopathy)

Kidney/skin biopsy (confirmation)

- Immunohistochemistry (labelled antibody applied to biopsy, viewed on slide)
 - Label usually identifies collagen alpha chains
 - Misfolded collagen degraded; does not stain

- Electron microscopy
 - **Early disease:** thinning of glomerular basement membrane
 - **Later disease:** glomerular basement membrane thin, thick, abnormal segments, **split lamina densa** (appears as woven basket)

Gene testing

- Gene testing for COL4A genes
 - Diagnostic procedure of choice due to noninvasive nature, accuracy

TREATMENT

MEDICATIONS

- Renal
 - Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers prevent progression to kidney failure, dialysis, kidney transplant

SURGERY

- Anterior lenticonus
 - Replacement of lens

OTHER INTERVENTIONS

- Hearing loss may benefit from hearing aids

EHLERS–DANLOS SYNDROME (EDS)

osms.it/ehlers-danlos_syndrome

PATHOLOGY & CAUSES

- **Defective collagen synthesis** → group of rare connective tissue disorders → tissue fragility
 - Single gene disorders
 - **Autosomal dominant/recessive**
 - 30 types of collagen may be affected
 - 13 different Ehler–Danlos syndromes classified on distribution of tissue involvement

CAUSES

- Gene mutation (specific gene varies depending on type) → defective fibrous proteins/enzymes → ↑ elasticity of tissues, structure, ↓ strength of tissues
- Minor injuries → gaping defects → repair difficult due to low tensile strength

RISK FACTORS

- Family history

COMPLICATIONS

- Colon, large artery, corneal rupture; retinal detachment, diaphragmatic hernias, premature arthritis; pregnancy complications (e.g. cervical insufficiency, premature rupture of membranes)

SIGNS & SYMPTOMS

- **Skin**
 - **Hyperextensive**, fragile, vulnerable to trauma; **easy bruising**; atrophic scars
- Ligament laxity
 - **Hypermobile joints**; joint dislocation predisposition (diagnosed by Beighton hypermobility scale); spinal malformations (e.g. scoliosis); osteochondrosis, arthritis; pain in muscles, joints
- Bones, joints
 - Pes planus, pectus excavatum, high arched palate; islocations
- Cardiovascular

- Spontaneous artery dissection; valvular disorders; arterial rupture; Raynaud's phenomenon; impaired platelet aggregation
- Spontaneous [organ rupture](#)
- Cerebrovascular rupture

DIAGNOSIS

OTHER DIAGNOSTICS

- Clinical exam
 - Typical presentation (e.g. lens dislocation, cardiovascular incidents, hypermobility)
 - Beighton score (evaluates hypermobility): nine criteria, four needed to establish hypermobility
- Ehler–Danlos specific genetic panel (confirmation)
- Skin biopsy



Figure 23.1 Hypermobility at the wrist and metacarpophalangeal joints in an individual with Ehlers–Danlos syndrome.

TREATMENT

MEDICATIONS

- According to type
 - *Pain medication*: nonsteroidal anti-inflammatory drugs (NSAIDs) for arthralgia, myalgia

SURGERY

- According to type
 - Joint surgery for severe arthritis

OTHER INTERVENTIONS

- According to type
 - Education, counseling
 - Physical therapy to prevent joint damage
 - Casting/orthoses to stabilize joints
 - Regular cardiovascular monitoring

MARFAN SYNDROME

osmosis.org/learn/marfan_syndrome

PATHOLOGY & CAUSES

- Genetic disorder of defective connective tissue

CAUSES

- Fibrillin 1 structural protein dysfunction due to *FBN1* gene mutation (locus 15q21)
 - Autosomal dominant
 - Compromised extracellular matrix (e.g. elastic fibers)
 - Fibrillin loss → ↑ transforming growth factor beta (TGF-β) → ↓ vascular muscle, extracellular matrix → compromises strength, elasticity → Marfanoid appearance
 - Skeleton, heart, blood vessels, eyes, lungs; most commonly affects aorta, ligaments, ciliary zonules supporting lens
- Hyperextensibility with inability to extend elbows 180°
 - Scoliosis
 - Pes excavatum, pigeon chest
 - Arachnodactyly (long fingers)
 - **Thumb sign:** thumb protrudes beyond ulnar margin when fist clenched
 - **Wrist sign:** entire fingernail of fifth finger covered by thumb when wrapped around wrist
 - Dolichocephaly
 - Narrow skull

RISK FACTORS

- Family history

COMPLICATIONS

- Lens dislocation, aortic rupture, pneumothorax

SIGNS & SYMPTOMS

- Vary in severity, rarely present at birth (neonatal Marfan syndrome)

Eyes

- Bilateral cranial, temporal dislocation of lens (ectopia lentis); highly specific
- Retinal detachment
- Downward slant of palpebral fissures

Skeleton

- Tall, slim with long (↑ arm span to height ratio); slender limbs
- Narrow, arched palate

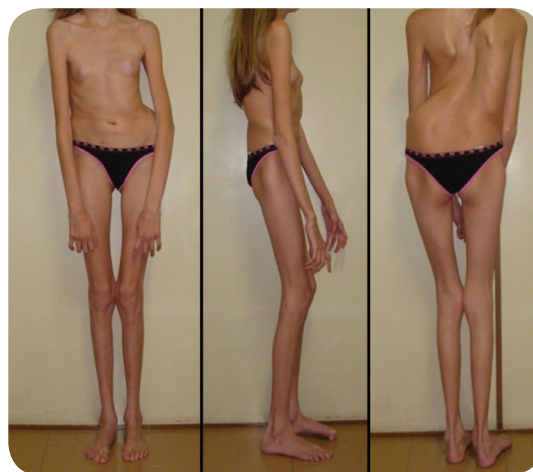


Figure 23.2 An adolescent female with Marfan syndrome. She is taller than average and thin, with long arms and legs. Arachnodactyly is also seen.

Heart

- Aortic root dilation, floppy valve syndrome (mitral valve), aortic dilation causes aortic valve insufficiency

Lungs

- Blebs, bullae (dilated spaces filled with air predisposing to spontaneous pneumothorax)

Blood vessels

- Cystic medial necrosis of aorta, aortic incompetence, dissecting aortic aneurysms

Skin

- Striae (stretch marks)

DIAGNOSIS**OTHER DIAGNOSTICS**

- History, physical exam
 - *Ghent nosology criteria*: scale using major, minor indicators to establish Marfan diagnosis, max 20 points; includes family history, skeletal, vascular, ocular, pulmonary/skin symptoms (e.g. ectopic lens and aortic dissection)
- Genetic testing
 - Confirmation of *FBN1* mutation

TREATMENT**MEDICATIONS**

- Beta blockers (slow aortic dilation)
- Angiotensin receptor blockers (decrease TGF- β signalling, slow aortic dilation)

SURGERY

- Valve, lens replacement; aortic dissection repair

OTHER INTERVENTIONS

- Physiotherapy
 - Restrict high-intensity exercise, scoliosis treatment
- Routine aortic, heart, ophthalmic screening

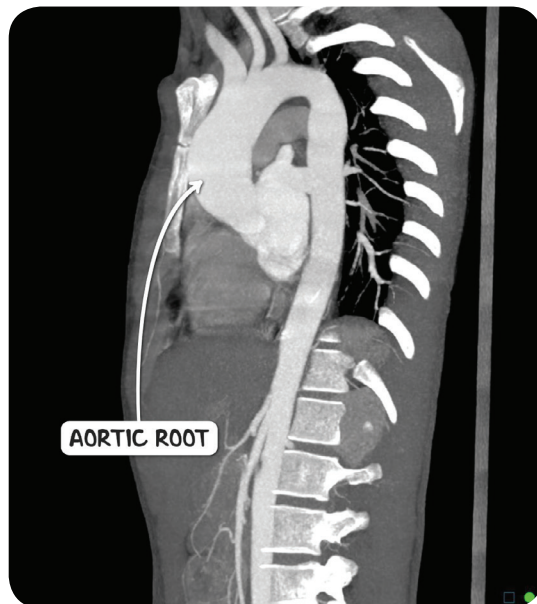


Figure 23.3 A contrast CT scan of the chest in the sagittal plane demonstrating aortic root dilation in an individual with Marfan syndrome.